PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of ~~Transmittal of International~~ Preliminary Examination Report (Form PCT/IPEA/416)
CEL62355PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/07848	18.07.2003	19.07.2002

International Patent Classification (IPC) or both national classification and IPC
C07K14/00

Applicant
CELLZOME AG ET AL.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.02.2004	11.08.2004

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07848

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-138 as originally filed

Claims, Numbers

1-45 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 22, 33, 34, 42-44

   because:

   ☒ the said international application, or the said claims Nos. 42-44 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 22, 33, 34

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-10, 12-21, 23-32, 35-41, 45
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21, 23-32, 35-41, 45
Industrial applicability (IA)	Yes:	Claims	1-21, 23-32, 35-41, 45
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 42-44 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of the present claims 42-44 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following **documents**:

D1: IKURA TSUYOSHI ET AL: 'Involvement of the TIP60 histone acetylase complex in DNA repair and apoptosis' CELL, vol. 102, no. 4, 18 August 2000 (2000-08-18), pages 463-473, XP002267408 ISSN: 0092-8674 cited in the application

D2: RIGAUT G ET AL: 'A generic protein purification method for protein complex characterization and proteome exploration' NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 17, no. 10, October 1999 (1999-10), pages 1030-1032, XP002179540 ISSN: 1087-0156 cited in the application

D3: WO 02 22660 A (HYSEQ INC ;WEHRMAN TOM (US); YANG YONGHONG (US); ZHANG JIE (US); Z) 21 March 2002 (2002-03-21)

D4: WO 01 57190 A (CAO YICHENG ;CHEN RUI HONG (US); GOODRICH RYLE (US); HYSEQ INC (US) 9 August 2001 (2001-08-09)

DISCLOSURE, CLARITY AND SUPPORT (Art. 5 and 6 PCT)

Claims 1-11, 13-21, 23-32, and 35-45 relate to 'derivatives', 'fragments' and 'homologs' defined by reference to a desirable characteristic or property, namely having the activity of the protein from which they were derived. In particular, claim 13 is directed to proteins named 'C20orf20' and 'KIAA1093 (Fragment)', which are of unknown function, while the claim extends to functional fragments and derivatives. The application provides no support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for any such variants. Independent of the above reasoning, the claims also lack clarity. An attempt is made to define the product by reference to a result to be achieved.

Said claims also relate to 'variants' of a protein, encoded by a nucleic acid which hybridises under low stringency conditions to the nucleic acid which encodes the protein of which they are variants. The number of 'variants' within the scope of such a claim is so large, that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises.

Claim 8 relates to a complex having a biochemical activity, namely transcriptional or apoptotic activity, where the only complex with such activity disclosed in the sense of Art. 5 PCT or supported in the sense of Art. 6 PCT in the application is the protein complex containing the complex members with SEQ ID NO: 1-18.

Claim 12 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed, namely polypeptides with SEQ ID NO: 1-18.

Claim 17 relates to an antibody or a fragment thereof which binds to a complex, but not to any of its uncomplexed components. The application provides no support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for any such antibodies. Independently, the claims also lack clarity. An attempt is made to define the product by reference

to a result to be achieved.

The vague and imprecise statement in the description on page 137 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

NOVELTY (Art. 33(2) EPC)

D1 discloses the purification of the TIP60 histone acetylase complex. A number of polypeptides of the complex have been characterised by using recombinant FLAG-HA epitope-tagged TIP60 to determine the bound polypeptides. The polypeptides have been identified inter alia as actin, BAF53, ECP-51/RUVLB2, TRRAP/ PAF400 and RUVLB1/ECP-54. It has to be considered that the TIP60 complex has not been fully characterised since 'at least 12 proteins ... specifically associate with TIP60'. and therefore some protein components are yet unidentified. Accordingly, such a TIP60 complex can be assumed to comprise the polypeptides of the present application (SEQ ID NO: 1-18), regardless of whether they had been identified as such at the time. It is therefore doubtful whether a TIP60 complex comprising the polypeptides with SEQ ID NO: 1-18 is new.

D2 discloses a process for preparing a complex (tandem affinity purification, TAP) comprising the following steps: expressing a double-tagged protein (bait) of the complex in a target cell, wherein the tags are separated by a protease cleavage site (TEV recognition sequence), isolation of the protein complex attached to the bait, dissociation of the complex and isolation of the individual complex members.

D3 discloses a nucleic acid encoding a polypeptide identical to SEQ ID NO: 4 and their use in therapy and diagnosis.

D4 discloses a nucleic acid encoding a polypeptide identical to SEQ ID NO: 11 and their use in therapy and diagnosis.

The subject-matter of claims 12-16, 23 and 24 encompasses individual com-

ponents of the complex, and more specifically 'C20orf20' and 'KIAA1093'. All of these proteins are known from the prior art, see e.g. D1, D3 and D4. Said claims are therefore not novel in the sense of Art. 33(2) PCT.

The present application does not meet the requirements of Article 33(2) because the subject-matter of claims 1-10, 12-21, 23-32, 35-41 and 45 is not new.

INVENTIVE STEP (Art. 33(3) PCT)

The subject-matter of claims 1-11, 18-21, 23-32, 35-41 and 45 extends to complexes comprising various combinations of individual protein(s) of the TIP60 complex with other individual protein(s) of that complex. It is not likely or obvious that such incomplete complexes have the same (transcriptional or apoptotic) or any other activity. It is at present not clear which problem these complexes solve. Accordingly, no inventive step can be attributed to these complexes of the invention.

Document D1 is considered to represent the most relevant state of the art and discloses a process for preparing a TIP60 complex using a double-tagged TIP60 polypeptide (see point 2).

The subject-matter of claim 11 differs in that the two tags are separated by a cleavage site for a protease, thereby permitting efficient recovery of the fusion proteins present at low concentrations in a complex mixture.

The problem to be solved by the present invention may therefore be regarded as the provision of a further process for preparing a TIP60 complex.

The solution is the provision of a process using two tags which are separated by a cleavage site for a protease.

This solution cannot however be considered as involving an inventive step for the following reasons:

The feature 'two tags separated by a cleavage site for a protease' is a matter of normal design procedure, see for example document D2. Its inclusion in the

process described in document D1 would therefore be an obvious design possibility for the skilled person in order to solve the problem posed.

In view of the above, the present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claim 11 does not involve an inventive step.